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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/615,497	HUANG, DOUG HUI	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *33-35 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32,36-42,44 and 45* is/are rejected.

7)☒ Claim(s) *32 and 45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0204*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I in the reply filed on May 9, 2006 is acknowledged. With regard to the restriction of the claims into Groups I-II, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 33-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 3, 2006.

3. Applicant's election with traverse of the polymorphisms CYP2D6*4, CYP2D6*5, and CYP2D6*Nx2 (and corresponding phenotypes) and of corresponding primers SEQ ID Nos 9, 14, and 11 in the reply filed on May 9, 2006 is acknowledged. In a supplemental response filed August 3, 2006, Applicant clarified that the claims readable on the elected invention are claims 1-32, 36-42, and 44-45.

It is noted that applicant's election specifies 3 polymorphisms without limiting the election to the combination of the three polymorphisms, and further, that the claims identified as readable on the elected invention include claims 44-45, which are not limited to a combination of the 3 elected polymorphisms (rather, e.g., claim 44 requires only SEQ ID NO: 11). Further, none of the pending claims specifically recite or are limited to a combination of the three elected polymorphisms. Accordingly, applicant's election has been treated as an election of any of the specified polymorphisms/primers as well as any combinations thereof.

Applicant's traversal is on the ground(s) that the requirement for a species election "attempts to divide the invention along the lines of the different polymorphisms identified by the method" and that "This attempt to divide on the basis of structural differences is not an appropriate basis for a species election in the present case, which provides unity of invention on the basis of a single method that can detect these different structural polymorphisms." Applicant's arguments have been thoroughly considered but are not found persuasive. Applicant's claims are not limited to a "single method that can detect" a variety of different structural polymorphisms, but rather encompass a vast number of different methods drawn to the detection of a variety of different polymorphisms and combinations thereof. As these different methods involve the detection of and use of a variety of different molecules lacking a common structure and common functional properties, the various methods encompassed by the claims do not meet the requirements for unity of invention. Further, each species encompassed by the claims requires a different sequence search and a different text search; thus, a search of multiple species would impose a serious burden. **Accordingly, the requirement is still deemed proper and is therefore made FINAL.** However, Applicant is reminded that upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim, as noted in the restriction requirement of March 27, 2006.

Priority

4. It is noted that as the claimed invention finds support in provisional application 60/393,967, the effective filing date of the instant application is July 5, 2002.

Information Disclosure Statement

5. The information disclosure statement filed January 22, 2004 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. Particularly, as document A5 is not in English and as no translation has been provided, only the English language abstract of the document has been considered.

Claim Objections

4. Claims 32 and 45 are objected to because of the following informalities. Claim 32 recites the "method of claim 31 or 32," such that the claim depends from itself. It appears that the claim was intended to depend from claim 30 or 31 (rather than 31 or 32). Claim 45 recites "ND" rather than "and." Appropriate correction is required.

Specification

5. The use of the trademarks GENBANK, ALPHAIMAGER, BIOMEK, QIAGEN, MICROAMP, GENEAMP, SEAKEM, and GENESCAN has been noted in this application. The trademarks should be capitalized wherever they appear.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-32, 36-42 and 44-45 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-18 and 30-32 are indefinite over the recitation of the limitations "said ddNTPs comprising a label" and "said detection primer" in step (a)(iv) of claim 1 because there is insufficient antecedent basis for these limitations in the claim.

Claims 1-18 and 30-32 are indefinite over the recitation of the limitation "relating the labeled nucleic acid to the identity of said polymorphism in said sample" in step (b) of claim 1. First, there is insufficient antecedent basis for the recitation "the labeled nucleic acid" because the claim previously refers to "at least one labeled nucleic acid" rather than to a particular labeled nucleic acid. Second, there is insufficient antecedent basis for the limitation "said polymorphism" because the claim previously refers to "polymorphisms" but not a particular "polymorphism." Further, it is noted that the prior step of the claim encompasses generating multiple labeled nucleic acids; it is not clear whether the "relating" step (which refers only to a single nucleic acid and a single polymorphism) encompasses detecting of multiple polymorphisms, or whether the claim

is limited to detection of "one" polymorphism (as recited in the preamble). Finally, it is not clear what is encompassed by the term "relating," and how this step relates to the act of "identifying" (which is required by the claim preamble). Does the claim in fact require identification of "one of a plurality of preselected polymorphisms," or does the claim merely require "relating" a labeled nucleic acid to a polymorphism? Clarification is required.

Claim 3 is indefinite over the recitation of the limitation "said amplification is accomplished by the addition of" primers. It is not clear whether this claim language requires "the addition" of primers to the reaction of step (a), or whether this language encompasses, e.g., the addition of primers to some other, separate amplification reaction.

Claims 4-5 are indefinite over the recitation of the limitation "said labeled nucleic acid(s)" in claim 4 because there is insufficient antecedent basis for this limitation in the claims.

Claim 6 is indefinite over the recitation of the limitation one or more of steps (a), (b) or (c), or combinations thereof" because claim 1, from which claim 6 depends, does not include a step "(c)". Further, it is not clear how the limitation "or combinations thereof" further limits the claim, as the claim already encompasses "one or more" of the steps. Clarification is required.

Claims 8-10 are indefinite over the recitation of the limitation "said plurality of preselected cytochrome P450 2D6 polymorphisms" (see claim 8 and claim 9). There is insufficient antecedent basis for this limitation in the claims.

Claim 8 is indefinite over the recitation of the language "independently selected." It is unclear how the term "independently" further limits the invention within the context of the claim; for example, how would a polymorphism "selected" from the recited group differ from one that is "independently selected?"

Claims 12-17 are indefinite over the recitation of the limitation "said polymorphism" in claim 12 because there is insufficient antecedent basis for this limitation in the claims.

Claims 13-14 are indefinite over the recitation of the limitation "said xenobiotic" in claim 13 because there is insufficient antecedent basis for this limitation in the claims.

Claims 15-17 are indefinite over the recitation of the limitation "said xenobiotic" in claim 15 because there is insufficient antecedent basis for this limitation in the claims.

Claims 19-32 are indefinite over the recitation of the limitation "relating the labeled nucleic acid to the identity of said polymorphism in said sample" in step (b) of claim 1. It is not clear what is encompassed by the term "relating," and how this step relates to the act of "identifying" (which is required by the claim preamble). Does the claim in fact require identification of a polymorphism or does the claim merely require "relating" a labeled nucleic acid to a polymorphism? Clarification is required.

Claims 20-21 are indefinite because it is unclear how the claims further limit claim 19. Particularly, while claim 20 appears to limit the manner in which nucleic acid is "obtained," claim 19 does not include or require obtaining nucleic acid (rather claim 19 includes a step in which labeled nucleic acid is "generated" from a sample).

Claim 21 is indefinite over the recitation of the limitation "said amplification is accomplished by the addition of" primers. It is not clear to what primers are added, and thus it is unclear how this claim limitation may be met.

Claims 22-25 are indefinite because it unclear how the claims further limit claim 19. Claim 19 as written requires a "labeled nucleic acid comprising a means for distinguishing amongst a plurality of" polymorphisms. However, claims 22 and 24 as written attempt to further limit the "means" by requiring particular method steps/method conditions. It is not clear how such limitations might further limit the structure or other properties of the "labeled nucleic acid" of claim 19.

Claim 26 is indefinite over the recitation of the limitation "said plurality of preselected cytochrome P450 2D6 polymorphisms" because there is insufficient antecedent basis for this limitation in the claims.

Claim 26 is indefinite over the recitation of the language "independently selected." It is unclear how the term "independently" further limits the invention within the context of the claim; for example, how would a polymorphism "selected" from the recited group differ from one that is "independently selected?"

Claims 27-28 are indefinite over the recitation of the limitation "said preselected cytochrome P450 2D6 polymorphisms" because there is insufficient antecedent basis for this limitation in the claims.

Claim 28 is indefinite over the recitation of the limitation "said extension primers" because there is insufficient antecedent basis for this limitation in the claims.

Claims 30-32 are indefinite because it is unclear how the claims further limit claims 1 and/or 19. Claims 30-31 each refer to "a cytochrome P450 2D6 genotype of said subject identified by the method of claim 1 or 19." However, as claims 1 and 19 are not drawn to identification of either a genotype or a subject, it is not clear how claims 30-32 further limit the methods of claims 1/19.

Claims 36-42 and 44-45 are indefinite over the recitation of the limitation "at least one of a preselected polymorphism" in claim 36. It is not clear whether this language is intended to refer to, e.g., multiple copies of a single polymorphism, or whether applicant's intent was to recite "at least one preselected polymorphism," etc.

Claims 36-42 and 44-45 are indefinite over the recitation of the limitations "said ddNTPs comprising a label," "said at least one detection primer," and "said preselected polymorphisms" in step (a)(iv) of claim 36 because there is insufficient antecedent basis for these limitations in the claim.

Claims 36-42 and 44-45 are indefinite over the recitation of the limitation "said at least one extension primer is distinctively labeled by addition of one of said ddNTPs comprising a label to the 5'-end of said at least one detection primer" in claim 36, step (a)(iv). It is noted that (as acknowledged in the specification at pages 8-9) primer extension involves enzymatic extension of the 3' (not 5') end of an extension primer. It is therefore unclear why the claim refers to addition of a ddNTP to the 5' end of the primer. As noted above, antecedent basis is also lacking for the recitation "said at least one detection primer." Accordingly, clarification of this method step is required.

Claims 36-42 and 44-45 are indefinite over the recitation of the limitation "relating the labeled nucleic acid to the identity of said polymorphism in said sample" in step (b) of claim 1. First, there is insufficient antecedent basis for the recitation "the labeled nucleic acid" because the claim previously refers to "at least one labeled nucleic acid" rather than to a particular labeled nucleic acid. Further, it is noted that the prior step of the claim encompasses generating multiple labeled nucleic acids; it is not clear whether the "relating" step (which refers only to a single nucleic acid and a single polymorphism) encompasses detection of multiple polymorphisms, or whether the claim is limited to detection of "one" polymorphism. Finally, it is not clear what is encompassed by the term "relating," and how this step relates to the act of "identifying" (which is required by the claim preamble). Does the claim in fact require identification of a polymorphism or does the claim merely require "relating" a labeled nucleic acid to a polymorphism? Clarification is required.

Claim 38 is indefinite over the recitation of the limitation "said amplification is accomplished by the addition of" primers. It is not clear whether this claim language requires "the addition" of primers to the reaction of step (a), or whether this language encompasses, e.g., the addition of primers to some other, separate amplification reaction.

Claims 39-40 are indefinite over the recitation of the limitation "said labeled nucleic acid(s)" in claim 39 because there is insufficient antecedent basis for this limitation in the claims.

Claim 41 is indefinite over the recitation of the limitation "one or more of steps (a), (b) or (c), or combinations thereof" because claim 36, from which claim 41 depends, does not include a step "(c)". Further, it is not clear how the limitation "or combinations thereof" further limits the claim, as the claim already encompasses "one or more" of the steps. Clarification is required.

Claims 44-45 are indefinite over the recitation of the limitation "said primers" because there is insufficient antecedent basis for this limitation in the claims. It is further noted that claim 44 recites only a single primer.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1-2, 4, 6-9, 11-20, 22, 24-27, and 29-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Anastasio et al (WO 02/38589 A2 [05/16/2002; filed 11/09/2001]), in light of the teachings of Goelet et al (WO 92/15712 [09/17/1992]).

It is noted that the portions of the Anastasio et al reference on which the instant rejection relies find support in provisional application 60/247,943, filed November 9, 2000.

Anastasio et al disclose methods of genotyping and haplotyping the CYP2D6 gene in which one or more of the polymorphisms present in the gene are detected (see entire reference). Anastasio et al disclose methods in which primer extension is employed to identify polymorphisms, and disclose "primer extension oligonucleotides" for use in their methods in which the 3' termini of the oligonucleotides are "complementary to the nucleotide located immediately adjacent to the polymorphism site" (see, e.g., pages 18 and 22-23, and claim 4). In these methods of Anastasio et al, isolated nucleic acids from an individual are amplified, and primer extension is performed on the amplified nucleic acids, wherein the identity of the terminator in the extended oligonucleotide is identified to determine the identity of the polymorphism(s) present (see, e.g., claim 4). While Anastasio et al do not refer to the use of "distinctively labeled ddNTPs" in their methods (as set forth in independent claim 1), Anastasio et al do disclose the use of the "polymerase-mediated primer extension method" of patent WO92/15712 (Goelet et al) in the identification of polymorphisms (page 23). Goelet et al teach that their method employs differently labeled terminators, such that the identification of the nucleotide at the position of interest may be established based on the identity of the detectable marker incorporated into the primer during extension (see entire reference, particularly pages 10-13 and 21-22, summarizing the primer extension method of Goelet et al). Thus, the Goelet et al reference provides extrinsic evidence that the primer extension method of Anastasio et al meets the limitations of, and anticipates, the claimed invention (see *MPEP* 2131.01).

With regard to independent claim 19 and claims dependent therefrom, it is noted that differently labeled terminators constitute a "means for distinguishing amongst a plurality" of polymorphisms that may be "related...to the identity" of polymorphisms in a sample, as required by the claims.

Regarding dependent claims 2 and 20, it is again noted that Anastasio et al disclose obtaining nucleic acids from a sample by amplification (see above).

Regarding dependent claims 4 and 22, it is noted that the method of Goelet et al (i.e., the method referenced in the Anastasio et al reference) requires identification of the detectable marker present on the terminator incorporated during primer extension (see, e.g., pages 11 and 22), and that Goelet et al teach subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43).

With respect to claims 6 and 24, Goelet et al disclose automated methods (see, e.g., page 51-52).

Regarding claims 7 and 25, Goelet et al disclose the labeling of each terminator with a different fluorophore (see, e.g., page 20).

Regarding claims 8-9, 18, 26-27 and 32, Anastasio et al disclose more than 40 polymorphisms of the CYP2D6 gene, including multiple polymorphisms encompassed by the claims, and disclose detection of numerous haplotypes/genotypes of CYP2D6, including the wild type gene (see entire reference). With regard to the polymorphisms elected by applicant, it is particularly noted that the polymorphism identified by Anastasio et al as "PS33" corresponds to CYP2D6*4 (see, e.g., page 4 and Figure 1B).

Regarding claims 12-17 and 30-32, Anastasio et al disclose that CYP2D6 is a "pharmaceutically-important" gene whose gene product is involved in metabolism of a variety of drugs including "antiarythmics, adrenoceptor antagonists, and trycyclic antidepressants," and teach that CYP2D6 genotype affects the extent to which a variety of drugs are metabolized in subjects (see, e.g., pages 1-3). With further regard to claims 30-32, Anastasio et al also teach the use of their genotyping/haplotyping methods in selecting appropriate drugs for treatment of a disease or condition (see, e.g., pages 7, 26-27).

Regarding claims 11 and 29, it is noted that the samples disclosed by Anastasio et al are human samples (see entire reference, particularly, e.g., the examples).

10. Claims 1-2, 4, 6-9, 11-20, 22, 24-27, and 29-32 are rejected under 35 U.S.C. 102(a) as being anticipated by Anastasio et al (WO 02/38589 A2 [05/16/2002; filed 11/09/2001]), in light of the teachings of Goelet et al (WO 92/15712 [09/17/1992])..

Anastasio et al disclose methods of genotyping and haplotyping the CYP2D6 gene in which one or more of the polymorphisms present in the gene are detected (see entire reference). Anastasio et al disclose methods in which primer extension is employed to identify polymorphisms, and disclose "primer extension oligonucleotides" for use in their methods in which the 3' termini of the oligonucleotides are "complementary to the nucleotide located immediately adjacent to the polymorphism site" (see, e.g., pages 18 and 22-23, and claim 4). In these methods of Anastasio et al, isolated nucleic acids from an individual are amplified, and primer extension is performed on the amplified nucleic acids, wherein the identity of the terminator in the

extended oligonucleotide is identified to determine the identity of the polymorphism(s) present (see, e.g., claim 4). While Anastasio et al do not refer to the use of "distinctively labeled ddNTPs" in their methods (as set forth in independent claim 1), Anastasio et al do disclose the use of the "polymerase-mediated primer extension method" of patent WO92/15712 (Goelet et al) in the identification of polymorphisms (page 23). Goelet et al teach that their method employs differently labeled terminators, such that the identification of the nucleotide at the position of interest may be established based on the identity of the detectable marker incorporated into the primer during extension (see entire reference, particularly pages 10-13 and 21-22, summarizing the primer extension method of Goelet et al). Thus, the Goelet et al reference provides evidence that the primer extension method of Anastasio et al meets the limitations of, and anticipates, the claimed invention (see *MPEP* 2131.01).

With regard to independent claim 19 and claims dependent therefrom, it is noted that differently labeled terminators constitute a "means for distinguishing amongst a plurality" of polymorphisms that may be "related...to the identity" of polymorphisms in a sample, as required by the claims.

Regarding dependent claims 2 and 20, it is again noted that Anastasio et al disclose obtaining nucleic acids from a sample by amplification (see above).

Regarding dependent claims 4 and 22, it is noted that the method of Goelet et al (i.e., the method referenced in the Anastasio et al reference) requires identification of the detectable marker present on the terminator incorporated during primer extension

(see, e.g., pages 11 and 22), and that Goelet et al teach subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43).

With respect to claims 6 and 24, Goelet et al disclose automated methods (see, e.g., page 51-52).

Regarding claims 7 and 25, Goelet et al disclose the labeling of each terminator with a different fluorophore (see, e.g., page 20).

Regarding claims 8-9, 18, 26-27 and 32, Anastasio et al disclose more than 40 polymorphisms of the CYP2D6 gene, including multiple polymorphisms encompassed by the claims, and disclose detection of numerous haplotypes/genotypes of CYP2D6, including the wild type gene (see entire reference). With regard to the polymorphisms elected by applicant, it is particularly noted that the polymorphism identified by Anastasio et al as "PS33" corresponds to CYP2D6*4 (see, e.g., page 4 and Figure 1B).

Regarding claims 12-17 and 30-32, Anastasio et al disclose that CYP2D6 is a "pharmaceutically-important" gene whose gene product is involved in metabolism of a variety of drugs including "antiarythmics, adrenoceptor antagonists, and trycyclic antidepressants," and teach that CYP2D6 genotype affects the extent to which a variety of drugs are metabolized in subjects (see, e.g., pages 1-3). With further regard to claims 30-32, Anastasio et al also teach the use of their genotyping/haplotyping methods in selecting appropriate drugs for treatment of a disease or condition (see, e.g., pages 7, 26-27).

Regarding claims 11 and 29, it is noted that the samples disclosed by Anastasio et al are human samples (see entire reference, particularly, e.g., the examples).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al in view of Dovichi and Zhang (Methods in Molecular Biology 167:225-239 [2001]; citation A20 of the IDS of 02/2004), in light of the teachings of Goelet et al.

Anastasio et al disclose methods of genotyping and haplotyping the CYP2D6 gene in which one or more of the polymorphisms present in the gene are detected (see entire reference). Anastasio et al disclose methods in which primer extension is employed to identify polymorphisms, and disclose "primer extension oligonucleotides" for use in their methods in which the 3' termini of the oligonucleotides are "complementary to the nucleotide located immediately adjacent to the polymorphism site" (see, e.g., pages 18 and 22-23, and claim 4). In these methods of Anastasio et al, isolated nucleic acids from an individual are amplified, and primer extension is performed on the amplified nucleic acids, wherein the identity of the terminator in the extended oligonucleotide is identified to determine the identity of the polymorphism(s) present (see, e.g., claim 4). While Anastasio et al do not refer to the use of "distinctively labeled ddNTPs" in their methods (as set forth in independent claim 1), Anastasio et al do disclose the use of the "polymerase-mediated primer extension method" of patent WO92/15712 (Goelet et al) in the identification of polymorphisms (page 23). Goelet et

al teach that their method employs differently labeled terminators, such that the identification of the nucleotide at the position of interest may be established based on the identity of the detectable marker incorporated into the primer during extension (see entire reference, particularly pages 10-13 and 21-22, summarizing the primer extension method of Goelet et al). Thus, the Goelet et al reference provides evidence of the steps and reagents involved in the primer extension method of Anastasio et al. It is further noted that the method of Goelet et al (i.e., the method referenced in the Anastasio et al reference) requires identification of the detectable marker present on the terminator incorporated during primer extension (see, e.g., pages 11 and 22), and that Goelet et al teach subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43). However, the Anastasio et al reference in light of the Goelet et al reference does not teach the use of capillary electrophoresis, as required by the instant claims.

Dovichi and Zhang teach that capillary electrophoresis (CE) allows for the more rapid determination of a DNA sequence as compared to conventional polyacrylamide gel electrophoresis (PAGE)(see entire reference, particularly pages 227-228). In view of the teachings of Dovichi and Zhang, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Anastasio et al so as to have subjected extended primers to CE rather than PAGE. An ordinary artisan would have been motivated to have made such a modification for the advantage of more rapidly determining the terminal base present in extended primers, as suggested by the teachings of Dovichi and Zhang.

13. Claims 10, 28, 36-37, 39, and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al in view of Pastinen et al (PCR Applications (1999), pages 521-535; Innis, M.A. et al, editors, Academic Press, San Diego), in light of the teachings of Goelet et al.

Anastasio et al disclose methods of genotyping and haplotyping the CYP2D6 gene in which one or more of the polymorphisms present in the gene are detected (see entire reference). Anastasio et al disclose methods in which primer extension is employed to identify polymorphisms, and disclose "primer extension oligonucleotides" for use in their methods in which the 3' termini of the oligonucleotides are "complementary to the nucleotide located immediately adjacent to the polymorphism site" (see, e.g., pages 18 and 22-23, and claim 4). In these methods of Anastasio et al, isolated nucleic acids from an individual are amplified, and primer extension is performed on the amplified nucleic acids, wherein the identity of the terminator in the extended oligonucleotide is identified to determine the identity of the polymorphism(s) present (see, e.g., claim 4). While Anastasio et al do not refer to the use of "distinctively labeled ddNTPs" in their methods (as set forth in independent claim 1), Anastasio et al do disclose the use of the "polymerase-mediated primer extension method" of patent WO92/15712 (Goelet et al) in the identification of polymorphisms (page 23). Goelet et al teach that their method employs differently labeled terminators, such that the identification of the nucleotide at the position of interest may be established based on the identity of the detectable marker incorporated into the primer during extension (see entire reference, particularly pages 10-13 and 21-22, summarizing the primer extension

method of Goelet et al). Thus, the Goelet et al reference provides evidence of the steps and reagents involved in the primer extension method of Anastasio et al.

Anastasio et al do not teach an extension primer having any of SEQ ID Nos 9-19, as required by the claims. It is again noted that Applicant elected SEQ ID Nos 9, 11, and 14 for examination.

Pastinen et al disclose a method of genotyping the CYP2D6 gene that accomplishes detection of multiple CYP2D6 alleles, including the elected CYP2D6*4 allele, by primer extension (see entire reference, particularly pages 529-530). The primer employed by Pastinen et al in detection of the CYP2D6*4 allele, primer 2D6*4 (see page 530), comprises the sequence identified by applicant as SEQ ID NO: 9.

In view of the teachings of Pastinen et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the primer extension method of Anastasio et al so as to have employed therein the 2D6*4 primer of Pastinen et al in embodiments of the method in which the detection of CYP2D6*4 was desired. As Anastasio et al do not exemplify detection of this allele using primer extension, and as Pastinen et al exemplify the successful use of their primer in detection the CYP2D6*4 allele, an ordinary artisan would have been motivated to have made such a modification (as opposed to, e.g., experimenting with various primers in order to identify an appropriate primer) for the advantage of more rapidly and conveniently achieving detection of CYP2D6*4.

14. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al in view of Pastinen et al, in light of the teachings of Goelet et al, as

applied to claims 10, 28, 36-37, 39, and 41-42, above, and further in view of Dovichi and Zhang.

It is further noted that the method of Goelet et al (i.e., the method referenced in the Anastasio et al reference) requires identification of the detectable marker present on the terminator incorporated during primer extension (see, e.g., pages 11 and 22), and that Goelet et al teach subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43). However, Anastasio et al and Pastinen et al, in light of the Goelet et al reference, do not teach the use of capillary electrophoresis, as required by the instant claims.

Dovichi and Zhang teach that capillary electrophoresis (CE) allows for the more rapid determination of a DNA sequence as compared to conventional polyacrylamide gel electrophoresis (PAGE)(see entire reference, particularly pages 227-228). In view of the teachings of Dovichi and Zhang, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Anastasio et al in view of Pastinen et al so as to have subjected extended primers to CE rather than PAGE. An ordinary artisan would have been motivated to have made such a modification for the advantage of more rapidly determining the terminal base present in extended primers, as suggested by the teachings of Dovichi and Zhang.

Conclusion

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. It is noted that the prior art as exemplified by, e.g., Sachse et al (American Journal of Human Genetics 60(2):284-295 [1997]) discloses methods

comprising the detection of multiple CYP2D6 variants, including CYP2D6*4, CYP2D6*5, and duplication alleles *1X2, *2X2, and *4X2 (see entire reference). However, the prior art does not teach or suggest methods employing SEQ ID NOS 11 and/or 14. It is further noted that while the prior art does teach methods employing, e.g., primers corresponding to SEQ ID NOS 1-2 (see Stuven et al, Pharmacogenetics 6(5):417-421 [1996]; citation A69 of the IDS of 02/2004) and primers corresponding to SEQ ID NOS 7-8 (see Johansson et al, Pharmacogenetics 6(4):351-355 [1996]), the prior art does not teach or suggest methods in which amplification is accomplished by the addition of all of SEQ ID NOS 1-8, as set forth in claims 3, 21, and 38.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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